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The Role of Tirzepatide in the Management of Obesity and Its Cardiometabolic Implications : A Review

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ABSTRACT

Obesity is a global health crisis closely linked to a spectrum of cardiometabolic disorders including Type 2 diabetes mellitus (T2DM), Hypertension, Dyslipidemia, and Cardiovascular disease (CVD). Tirzepatide, a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, has emerged as a promising therapeutic agent for obesity management. By leveraging the synergistic effects of GIP and GLP-1 pathways, tirzepatide has demonstrated superior efficacy in promoting weight loss, improving glycemic control, and modulating key metabolic parameters compared to existing monotherapies. This review explores the pharmacological mechanisms of tirzepatide, summarizes clinical trial outcomes, and evaluates its impact on obesity-related cardiometabolic outcomes.

Keywords: Obesity, Tirzepatide, GLP-1, GIP.

INTRODUCTION

Obesity is a health condition marked by an abnormal or excessive buildup of body fat that can negatively affect overall health (1). The epidemic not only contributes to a significant decline in quality of life and increased mortality but also places a substantial burden on healthcare systems (2). Obesity is intrinsically linked to the development of a range of cardiometabolic conditions, including Type 2 diabetes mellitus (T2DM), Hypertension, Dyslipidemia, Non-alcoholic fatty liver disease (NAFLD), and Cardiovascular disease (CVD), all of which increase the risk of premature death (3).

Tirzepatide, a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, has garnered significant attention (4,5). Unlike traditional monotherapy targeting GLP-1 alone, tirzepatide's dual agonism offers a unique therapeutic mechanism that enhances insulin secretion, delays gastric emptying, reduces appetite, and promotes weight loss(6,7).

Clinical trials such as the SURMOUNT and SURPASS programs have demonstrated tirzepatide's efficacy in achieving substantial and sustained weight loss in individuals with obesity, with or without diabetes (8). Beyond weight reduction, emerging evidence suggests that tirzepatide may favorably influence various cardiometabolic parameters, including glycemic control, lipid profiles, blood pressure, and markers of inflammation (9).

PATHOPHYSIOLOGY OF OBESITY AND CARDIOMETABOLIC RISKS

The pathophysiology of obesity is intricately linked to the development of insulin resistance, dyslipidemia, hypertension and systemic inflammation, all of which contribute to the increased risk of cardiometabolic diseases.

- **Insulin Resistance:** The excess adiposity, particularly visceral fat, leads to an increase in the release of free fatty acids (FFAs) and pro-inflammatory cytokines, which interfere with insulin signaling. These factors lead to higher circulating insulin levels (hyperinsulinemia) and impaired glucose uptake, increasing the risk of developing T2DM (10).

- **Dyslipidemia:**Dyslipidemia is characterized by elevated levels of triglycerides and low-density lipoprotein cholesterol (LDL-C), along with reduced levels of high-density lipoprotein cholesterol (HDL-C). Visceral

adipose tissue, especially in the abdominal region, releases large quantities of free fatty acids (FFAs) into the circulation.FFAs contribute to the liver's overproduction of very low-density lipoprotein cholesterol (VLDL) and the alteration of lipid metabolism. This lipid imbalance increases the risk of developing atherosclerosis, which is a precursor to coronary artery disease (CAD) and stroke (11).

- **Hypertension:** Excess adipose tissue leads to increased plasma volume due to enhanced sodium retention, as well as increased secretion of angiotensinogen, a precursor to angiotensin II which increase BP. Moreover, adipose tissue also secretes adipokines, such as leptinandresistin**,** which can directly influence vascular tone, contributing to the development of hypertension (12).

- **Systemic Inflammation:** Adipose tissue, especially visceral fat, secretes various pro-inflammatory cytokines, including tumornecrosis factor-alpha (TNF-α),interleukin-6 (IL-6) and C-reactive protein (CRP). These molecules promote endothelial dysfunction, insulin resistance, and increased risk of atherosclerosis. The inflamed adipocytes also release adipokines such as leptin, which, in excess, contributes to insulin resistance and the promotion of atherosclerotic plaques (13).

- **Adipose Tissue Dysfunction:** In obesity, especially visceral adiposity, the hypertrophied adipocytes exhibit altered secretion of adipokines (e.g. leptin, adiponectin, resistin) and FFAs. Leptin, typically involved in appetite regulation and energy balance, becomes ineffective in obese individuals due to leptin resistance. This leads to overeating, due to persistent hunger hormones. Conversely, adiponectin, which has anti-inflammatory and insulin-sensitizing properties, is reduced in obesity, contributing to insulin resistance. The dysregulated secretion of these molecules fosters a vicious cycle of metabolic disturbances (14).

- **Hormonal Imbalance:** Obesity disrupts the balance of several key hormones involved in appetite regulation and metabolic control. For instance, in addition to leptin resistance, there is an overproduction of ghrelin, the hunger hormone, which enhances appetite and food intake. Additionally, insulin, as discussed earlier, becomes less effective in obese individuals, further promoting glucose intolerance and worsening obesity. The imbalance between these hormones leads to increased fat accumulation, poor energy utilization, and further exacerbation of insulin resistance (15).

- **Gut-Brain Axis**: The gut-brain axisexplores how signals from the gastrointestinal tract influence appetite and energy balance. In obesity, alterations in gut microbiota composition and function can disrupt normal signaling pathways involved in satiety and hunger. Incretin hormones, such as GLP-1 and GIP, are released from the intestines and regulate insulin secretion, appetite, and gastric emptying. In obesity, the sensitivity of these hormones may be impaired, contributing to increased food intake and impaired glucose regulation. The introduction of dual agonists like tirzepatide, which target both GLP-1 and GIP receptors, offers a novel way to restore the dysregulated gut-brain axis and improve insulin sensitivity and weight loss (16).

MECHANISM OF ACTION

Tirzepatide activates both glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, which act as dual receptor agonist. These receptors play key roles in postprandial glucose regulation (17). By stimulating GLP-1 receptors, tirzepatide enhances glucose-dependent insulin secretion, suppresses inappropriate glucagon release, and slows gastric emptying—all of which contribute to better control of post-meal glucose excursions (18). The activation of GIP receptors further augments insulin secretion and improves glycemic regulation through additional metabolic pathways (19). Together, these actions result in significant reductions in fasting and postprandial blood glucose levels, and marked improvements in HbA1c, making tirzepatide highly effective for glycemic control in both diabetic and non-diabetic individuals (20).

Effect on Insulin Sensitivity

Beyond its insulinotropic effects, tirzepatide improves insulin sensitivity, a key factor in reversing metabolic dysfunction in obesity and type 2 diabetes (21). This improvement is partly driven by reductions in visceral fat mass, which is known to impair insulin signaling (22). Tirzepatide also exerts anti-inflammatory effects, reducing levels of pro-inflammatory cytokines that contribute to insulin resistance (23). Additionally, it modulates the secretion of adipokines such as adiponectin, which enhances insulin action in peripheral tissues(24). These mechanisms collectively improve insulin responsiveness in the liver, muscle, and adipose tissue, contributing to more efficient glucose uptake and utilization (25).

Effect on Satiety

Tirzepatide significantly influences appetite regulation through central nervous system pathways (26). It promotes satiety and decreases hunger by stimulating GLP-1 and GIP receptors in the brain, especially within the hypothalamus (27).The drug also delays gastric emptying, which prolongs the feeling of fullness after meals and supports appetite

suppression (28). These effects are crucial in promoting adherence to reduced-calorie diets and sustaining long-term weight loss (29).

Effect on Energy Intake

The reduction in energy intake observed with tirzepatide is primarily a consequence of its appetite-suppressing effects(30).Due to hunger suppression, individuals naturally consume fewer calories throughout the day (30).This reduction in caloric intake leads to a negative energy balance, facilitating progressive and sustained weight loss (31).Moreover, tirzepatide has been shown to alter food preferences in some individuals, leading to decreased desire for calorie-dense, high-fat, and sugary foods (31).This modification in eating behavior reinforces the drug's potential in treating obesity, not just by improving metabolic function but by reshaping dietary habits as well (32).

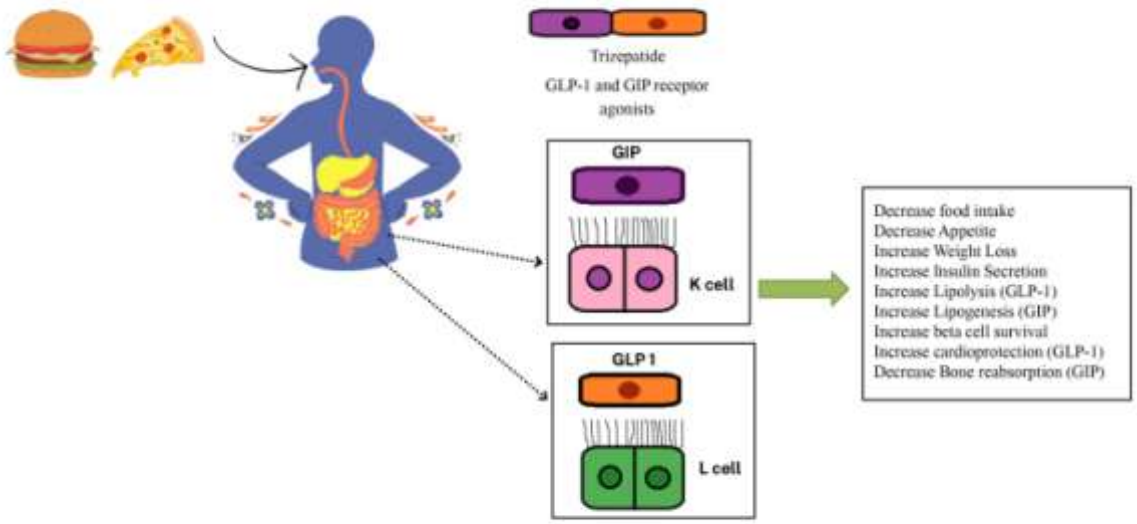

Figure 1. Mechanism of action of tirzepatide within the body.

CURRENT INDICATIONS

Tirzepatide is used alongside diet and exercise to help improve blood sugar control in adults with type 2 diabetes. It is used in managing obesity or weight-related conditions, including high blood pressure, type 2 diabetes, or abnormal cholesterol levels (33).

PHARMACOKINETICS

Tirzepatide is a dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors with a long-acting pharmacokinetic profile that enables once-weekly dosing (34). Following subcutaneous administration, tirzepatide reaches its maximum plasma concentration (Tmax) within approximately 8 to 72 hours. It has a long elimination half-life of about 5 days, which allows for sustained therapeutic effects over a weekly interval (35). The drug is mainly broken down by proteolytic cleavage of its peptide backbone and β-oxidation of its fatty acid side chain with involvement of the cytochrome P450 system (36). Tirzepatide displays dose-proportional pharmacokinetics over a wide range of doses, and steady-state concentrations are typically achieved within 4 to 5 weeks of once-weekly administration (37).

PHARMACODYNAMICS

Tirzepatide exerts its effects by simultaneously activating GIP and GLP-1 receptors, which are involved in the regulation of glucose metabolism and energy balance (38). This dual receptor activity enhances insulin secretion in a glucose-dependent manner, suppresses glucagon release, slows gastric emptying, and reduces appetite (39). These mechanisms contribute to improved glycemic control and significant weight reduction in individuals with type 2 diabetes. The drug also leads to improved insulin sensitivity and beta-cell function over time (40). Glucose-lowering and weight-reducing effects of tirzepatide have been shown to be superior than those of selective GLP-1 receptor agonists (41).

SIDE EFFECTS

Tirzepatide is generally well-tolerated, but like other GLP-1 receptor agonists, it is associated with a range of gastrointestinal side effects (42). The most common adverse effects include nausea, vomiting, diarrhea, decreased appetite, and constipation, particularly during the dose-escalation phase (43). Side effects include dizziness, fatigue and

localized reactions at the injection area (44). In rare cases, tirzepatide may be associated with more serious effects such as pancreatitis, gallbladder disease, and hypersensitivity reactions (45). Additionally, there may be an increased risk of hypoglycemia when used in combination with insulin or sulfonylureas (46).

CONTRAINDICATIONS

Tirzepatide should not be used in patients with medullary thyroid carcinoma (MTC) or those with multiple endocrine neoplasia syndrome type 2 (MEN 2).(47, 48). patients with a known hypersensitivity to drug or any of its components are contraindicated. (49). Caution is also advised in patients with a history of pancreatitis or severe gastrointestinal disease, such as gastroparesis (50). Medication is not recommended during pregnancy or breastfeeding (51).

CLINICAL TRIALS CONDUCTED ON TIRZEPATIDE IN CARDIOMETABOLIC IMPLICATION WITH OR WITHOUT DIABETES

The SURMOUNT-1 trial was a 72-week, phase 3, double-blind, randomized, placebo-controlled study evaluating tirzepatide in adults with obesity (BMI ≥30) or overweight (BMI ≥27) without diabetes. Weekly subcutaneous doses of tirzepatide at 5 mg, 10 mg, or 15 mg, or a placebo, were administered to participants, leading to an average weight loss of up to 20.9%, compared to 3.1% in the placebo group. Moreover, cardiometabolic improvements were observed (52).

The SURMOUNT-2 trial assessed the effectiveness of tirzepatide in individuals with obesity or overweight who also had type 2 diabetes. During the 72-week period, participants receiving 10 mg and 15 mg doses experienced mean weight reductions of 13.4% and 15.7%, respectively, while those on placebo saw a reduction of 3.3%. Additionally, the study showed marked improvements in glycemic control (HbA1c reduction) and cardiometabolic markers such as LDL cholesterol and triglycerides, affirming tirzepatide's dual benefit in managing obesity and diabetes (53).

The SURMOUNT-3 trial investigated tirzepatide in adults who had achieved ≥5% weight loss through a 12-week intensive lifestyle intervention. Over the course of 72 weeks, participants were randomized to receive either tirzepatide or placebo, with the tirzepatide group achieving an additional mean weight loss of 18.4%, compared to 2.5% in the placebo group. Notably, improvements were also observed in fasting insulin, triglycerides, and inflammatory markers, highlighting its benefit beyond weight reduction (54).

SURMOUNT-4 was a 112-week trial in which participants first received tirzepatide open-label for 36 weeks and achieved substantial weight loss (mean 20.9%). Participants who remained on tirzepatide sustained or experienced additional weight loss, whereas those switched to placebo regained 14% of their body weight. The study reinforces the need for ongoing treatment to sustain weight loss and metabolic benefits (55).

Table 1 : Various clinical trials conducted on Tirzepatide.

SL. NO	TITLE	AUTHORS	YEAR	SAMPLE SIZE	METHODOLOGY	RESULT
1	Tirzepatide Once Weekly for the Treatment of Obesity.	Ania M. Jastreboff et al.	2022	2,539	72-week, randomized, double-blind, placebo-controlled trial; non-diabetic adults with obesity or overweight received tirzepatide (5/10/15 mg) or placebo.	Up to 20.9% weight lossin 15 mg group vs. 3.1% with placebo; improvements in blood pressure, lipids, waist circumference.
2	Tirzepatide Once Weekly for the Treatment of Obesity in People with Type 2 Diabetes.	Rubino DM et al.	2023	938	72-week, randomized, placebo-controlled phase 3 trial in adults with obesity or overweight and type 2 diabetes.	Weight loss of 13.4–15.7% with tirzepatide vs. 3.3% with placebo; improved HbA1c and cardiometabolic markers.
3	Tirzepatide After Intensive Lifestyle Intervention in Adults with Obesity.	Wadden TA et al.	2023	806	Adults with ≥5% weight loss from a 12-week lifestyle intervention were randomized to tirzepatide or placebo for 72 weeks.	Additional 18.4% weight loss with tirzepatide vs. 2.5% with placebo; better insulin sensitivity and lipid profiles.

4	Effect of Continued Tirzepatide vs Placebo on Weight Regain in Adults with Obesity.	Rosenstock J et al.	2024	783	36-week open-label tirzepatide run-in followed by 52-week randomized, double-blind continuation vs. placebo.	Continued tirzepatide led to sustained or additional weight loss; placebo group regained ~14% of body weight.

CONCLUSION

Tirzepatide represents a promising advancement in the management of obesity, offering significant weight loss and improving cardiometabolic health. Its dual action on GLP-1 and GIP receptors not only enhances glycemic control but also favorably impacts lipid profiles, blood pressure, and inflammatory markers. Clinical evidence highlights tirzepatide's potential to reduce the risk of obesity-related complications, such as type 2 diabetes and cardiovascular disease. As ongoing research continues to explore its long-term effects and safety, tirzepatide may become a cornerstone in obesity treatment, offering a multifaceted approach to addressing the global obesity and cardiometabolic crisis.

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